REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claims 18, 38, 42 and 97 have been amended as suggested by the Examiner. This amendment is supported in the specification at page 6, line 31. Regarding claim 78, the claim has been revised to correct a typographical error. This amendment is supported in the specification at page 14, line 19.

Regarding claim 95, the term "about" has been removed.

Applicant acknowledges with thanks the acknowledgment and approval of the Substitute Specification with Abstract and Oath previously filed.

The remaining issue is a rejection of the claims under obviousness-type double patenting over the claims of USP 5,700,637 or the claims of USP 6,054,270, or a provisional rejection of the claims over the claims of co-pending applications Serial Nos. 09/300,279; 09/498,029; 09/619,645, 09/422,803; and 09/691,223.

There are submitted herewith Terminal Disclaimers which are believed to overcome each of these grounds of rejection.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version with markings to show changes made**".

In view of the foregoing, it is believed that each ground of rejection has been overcome. Favorable reconsideration and allowance is solicited.

Respectfully submitted,
Edwin Southern

By: _____
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Applicant

WMC/dlk
Washington, D.C. 20006-1021
Telephone (202) 721-8200
August 28, 2001

Version with Markings to Show Changes Made

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Edwin Southern :

Serial No. 09/422,804 : Group Art Unit 1631

Filed October 22, 1999 : Examiner A. Marschel

ANALYSING POLYNUCLEOTIDE SEQUENCES

AMENDMENT

Assistant Commissioner for Patents,
Washington, D.C.

Sir:

Responsive to the Official Action dated June 6, 2000, the time for responding thereto being extended for three months in accordance with a petition for extension submitted concurrently herewith, please amend the above-identified application as follows:

IN THE CLAIMS

Cancel without prejudice claim 1 and substitute therefor the following new claims:

-- 17. An array of oligonucleotides comprising a support having an impermeable surface to which a plurality of oligonucleotides are attached, the oligonucleotides having different nucleotide sequences and being attached at different known locations on the surface of the support, wherein the oligonucleotide at one known location is different from the oligonucleotide at another known location.

18. (Amended) An array of oligonucleotides comprising a support having a surface to which the oligonucleotides are attached, wherein oligonucleotides having different nucleotide sequences are attached at between 72 and 10^{12} different known locations on the surface of the support.

~~36. The array of claim 19, wherein the gene is selected from the DMD gene, the HPRT gene, the Huntington's disease gene and the cystic fibrosis gene.~~

~~37. The array of claim 17, 18 or 19, wherein one part of each oligonucleotide has a predetermined sequence and another part is made up of all possible sequences.~~

38. (Amended) The array of claim 17, wherein the oligonucleotides having different nucleotide sequences are attached from 72 to 10^{12} different locations on the surface of the support.

~~39. The array of claim 17, 18 or 19, wherein each oligonucleotide is attached by a covalent link through a terminal nucleotide residue on the surface of the support.~~

~~40.~~ A method of making an array of oligonucleotides, ~~which comprises~~:

attaching a plurality of oligonucleotides to an impermeable surface of a support, the oligonucleotides having different predetermined sequences and being attached at different known locations on the surface of the support,

wherein the oligonucleotides are synthesized before attachment to the surface of the support.

41. A method of making an array of oligonucleotides, which comprises:

attaching a plurality of oligonucleotides to an impermeable surface of a support, the oligonucleotides having different predetermined sequences and being attached at different known locations on the surface of the support,

~~wherein the oligonucleotides are synthesized in situ on the surface of the support.~~

42. (Amended) A method of making an array of oligonucleotides, which comprises attaching oligonucleotides to a surface of a support, the oligonucleotides having different predetermined

sequences and the oligonucleotides being attached at between 72 and 10^{12} different known locations on the surface of the support.

43. The method of claim 42, wherein the surface of the support is impermeable.

44. The method of claim 40, 41 or 42, wherein the different known locations are spaced apart by 10-100 μm.

45. The method of claim 40, 41 or 42, wherein the different oligonucleotides constitute part or all of a complete set of oligonucleotides of a predetermined length.

46. The method of claim 40, 41 or 42, wherein the entire nucleotide sequence of each oligonucleotide is predetermined.

47. The method of claim 40, 41 or 42, wherein the oligonucleotides are attached at the different known locations using a computer-controlled application device.

48. The method of claim 40, 41 or 42, wherein the oligonucleotides are attached using an ink-jet printer or pen plotter.

49. The method of claim 48, wherein the pen plotter includes a component including a polytetrafluoroethylene tube.

50. The method of claim 48, wherein the pen plotter is moved into position and the pen is lowered to lay down a coupling solution.

~~77. The method of claim 63, 64 or 68, wherein hybridisations are detected by means of a digitizing scanner.~~

78. (Amended) The method of claim 63, 64 or 68, wherein hybridizations are detected by means of a device having a resolution of between 1 µm and ~~125~~ 25 µm.

79. The method of claim 63, 64 or 68, wherein the oligonucleotides of the array constitute all or part of a complete set of oligonucleotides of predetermined length.

80. The method of claim 47, 48 or 52, which comprises using an array of oligonucleotides segregated such that the different regions have different base compositions to compensate for the differences in stability of duplexes of differing base composition.

81. The method of claim 80, in which the array is further segregated during hybridisation so that each area is exposed to different hybridisation conditions.

82. The method of claim 63, 64 or 68, wherein the polynucleotide is applied to the array under hybridisation conditions in the presence of a quaternary or tertiary amine.

83. The method of claim 82, wherein the amine is tetraethylammonium chloride used at a concentration in a range of 2M to 5.5M.

84. The method of claim 63, 64 or 68, wherein for analysing a polynucleotide of length N, there is used an array of oligonucleotides of length s, where 4^s is an order of magnitude greater than N.

85. The method of claim 63, 64 or 68, wherein the hybridisation temperature is chosen to be close to the Tm of duplexes and is controlled to better than ±0.5°C.

applying the polynucleotide to a substrate having an impermeable surface to which are immobilised a plurality of oligonucleotide probes having different predetermined sequences under hybridisation conditions, wherein the probes are immobilised at different known locations on the surface of the support such that the oligonucleotide at one known location is different from the oligonucleotide at another known location,

detecting the oligonucleotide probes to which the polynucleotide hybridizes, and

determining the sequence of the polynucleotide based upon the known sequence of the oligonucleotide probe to which the polynucleotide hybridizes.

92. The method of claim 91, wherein the polynucleotide is labelled.

93. The method of claim 91, wherein a plurality of polynucleotides are applied to the substrate.

94. The method of claim 93, wherein the plurality of polynucleotides are fragments of a gene.

95. (Amended) A method for analysing multiple sequence variants in multiple polynucleotides, which comprises:

a) laying down stripes of oligonucleotides corresponding to each sequence variant on the surface of a solid support,

b) applying the polynucleotides to the surface under hybridisation conditions in stripes orthogonal to those of the oligonucleotides, and

c) observing hybridisation at a site of intersection as an indication of the presence of a variant sequence in the polynucleotide,

wherein the stripes of oligonucleotides have a width of 1 mm or less and the polynucleotides are applied in orthogonal stripes ~~about~~ 5 mm wide.

96. A kit for analysing a polynucleotide comprising: an array of oligonucleotides comprising a support having an impermeable surface to which a plurality of oligonucleotides are attached, the oligonucleotides having different nucleotide sequences and being attached at different known locations on the surface of the support; apparatus for hybridisation of the polynucleotide to the array; and a scanner for detecting hybridisation.

(Amended)

97. A kit for analysing a polynucleotide comprising: an array of oligonucleotides comprising a support having a surface to which the oligonucleotides are attached, wherein oligonucleotides having different nucleotide sequences are attached at between 72 and 10^{12} different known locations on the surface of the support; apparatus for hybridisation of the polynucleotide to the array; and a scanner for detecting hybridisation.

98. A kit for analysing mutations of a gene comprising: an array of oligonucleotides having a known nucleotide sequence comprising a support having an impermeable surface to which are attached at different known locations a set of overlapping or partly overlapping or non-overlapping oligonucleotides which are complementary to a segment of the known nucleotide sequence of the gene; apparatus for hybridisation of the polynucleotide to the array; and a scanner for detecting hybridisation.

99. The kit of claim 96, 97 or 98, including also computer software and/or computer hardware for analysing the results. --

IN THE SPECIFICATION

Cancel without prejudice pages 1-30 of the specification as filed and substitute therefor the attached substitute specification containing pages 1-21.

Furthermore, please amend the substitute specification as filed.

Page 1, line 2, delete in its entirety and insert: